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Efficacy of Uridine Monophosphate, Acetyl-L-Carnitine and Alpha Lipoic Acid in the Treatment of Pain in Chronic Neuropathy and Radiculopathy: A Review of the Literature and an Observational Pilot Study on Radiculopathy

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Abstract

Peripheral neuropathy and radiculopathy are frequently observed conditions in outpatients primary care and can cause significant discomfort and functional deficits with strong impact on quality of life. The role of nutraceutics and supplements as additional tool for treating chronic pain has grown up in popularity in the past 10 years. Uridine monophosphate as well as acetyl_L-carnitine and also alpha lipoic acid have shown efficacy in treatment of pain due to neuropathies and symptomatic peripheral entrapments. In this survey a review of the literature is reported. In addiction, based on the cited evidences on efficacy of these ingredients in treatment of NP, an observational pilot study to evaluate the efficacy of combined Uridine Monofosphate, acetyl-L-carnitine and Alpha-lipoic-acid in reducing pain even in chronic radiculopathy is presented.

Keywords: Uridine Monophosphate; Acetyl-L-Carnitine; Radiculopathy; Chronic Pain

Abbreviations: NP: Neuropathic Pain, UTP: Uridine 5'-Triphosphate, CTP: Cytidine Triphosphate, PC: Phosphatidylcholine, PE: Phosphatidylethanolamine, ALC: Acetyl-L-Carnitine, PNP: Peripheral Neuropathic Pain, VAS: Visual Analogue Scale, ALA: Alpha-Lipoic-Acid

Background

Neuropathic pain (NP) is a condition resulting from damage or dysfunction of the somatosensory nervous system pathways, often described as a burning, stabbing or electric like excruciating pain **[1]**. It can be associated to various causes including diabetes mellitus, multiple sclerosis, trigeminal neuralgia, entrapment syndromes, exposure to neurotoxicants, alcoholism, chemotherapy and radiotherapy, compression or damage to nerve roots or nerves **[2]**. Positive or negative sensory symptoms (hyperalgesia, allodynia, hypoesthesia) may occur **[3,4]**. A detailed medical history, physical examination and electrophysiological invastigations

lead to a correct diagnosis **[4]**. NP has been emphasized on largely for its predominant unpleasant feeling, and has a strong impact on quality of life **[5]**. Management of NP consists of drug therapy and interdisciplinary approaches, but unfortunately, although substantial efforts have been made in recent years to develop efficacious medication and several new anti-neuropathic drugs have been introduced into the therapy, a real breakthrough has not been achieved **[6,7]**. Consequently, there is still a considerable need to explore novel treatment modalities. Pharmacological treatment of NP usually provides use of association of ingredients and molecules that act on different assets of pathology. Primary goal is to reduce pain to improve the quality of life. The superficial dorsal horn of the spinal cord plays an important role in sensory transmission, including information on pain signaling from the periphery. A proof of evidence has indicated the involvement of various neurotransmitters or neuromodulators released from primary afferent terminals, such as glutamate, substance P, and calcitonin gene related peptide **[8]**. Recently, ATP has been also proposed as another neurotransmitter or neuromodulator for spinal pain signaling **[9-11]**. Extracellular ATP acts on specific receptors, designated as P2 nucleotide receptors, at the cell surface. P2 nucleotide receptors are classified into two subfamilies, ligand-gated, ionotropic P2X receptors and G protein-coupled, metabotropic P2Y receptors, on the basis of their structures and signal transduction systems. Just few informations are known about the involvement of P2Y receptors in spinal pain transmission. Recently, Okada et al. **[12]** reported that ATP and Uridine 5'-triphosphate (UTP), a P2Y receptor agonist, inhibited the slow depolarization of substantia gelatinosa neurons evoked by repetitive stimulation of C-fibers of the dorsal root using adult rat spinal cord transverse slices with the dorsal root attached, suggesting that activation of P2Y receptors inhibited spinal pain transmission **[13]**. Furthermore, Okada et al. **[12]** demostrated analgesic acivity of uridine; they showed that UTP had a mechanical and thermal antinociceptive effects in normal rats and antiallodynic effects in a neuropathic pain model. In 2010 was explained pharmacodinamic action of Uridine on pain. Andò et al. **[14]** compared the analgesic activity of antagonists acting at P2X1, P2X7, and P2Y12 receptors and agonists (as UTP) acting at P2Y1, P2Y2, P2Y4, and P2Y6 receptors in neuropathic, acute, and inflammatory pain. They demonstrated that UTP (and other ligands) significantly alleviated mechanical allodynia in the neuropathic pain model and has a dose-dependent analgesic action in acute pain. Their results show that antagonism at P2X1, P2Y12, and P2X7 receptors and agonism at P2Y1 receptors define promising therapeutic strategies in acute, neuropathic, and inflammatory pain respectively. The circulating pyrimidines uridine and cytidine, besides being incorporated into nucleic acids, can serve as substrates for the salvage pathway of pyrimidine nucleotide synthesis; as precursors of the cytidine triphosphate (CTP) needed in the phosphatidylcholine (PC) and phosphatidylethanolamine (PE) biosynthetic pathway **[15]** and as precursors for the UDP (uridine diphosphate) and UTP (uridine triphosphate) that activate brain P2Y receptors **[16]** and that promote brain glycogen synthesis via UDPglucose **[17]**. Uridine did not initially attract attention as a precursor for PC synthesis by Kennedy pathway. However, recent studies exploring the effect of uridine on the levels of phospholipid intermediates have shown that uridine, by crossing the rat BBB via the CNT2 transporter, is taken up by the rat brain more efficiently than cytidine under physiological conditions and that it contributes to brain phosphatidylcholine and phosphatidylethanolamine synthesis via the Kennedy pathway **[18,19]**. All these informations attribute to Uridine a strategic therapeutic role on neuropathic pain **[20,21]**. A long-know molecule used in treatment of Neurophatic pain is Acetyl-L-carnitine (ALC). ALC is an ester produced by the human brain, liver, and kidney. ALC seems to increase the uptake of Acetyl-CoA into the mitochondria and exerts cholinomimetic effects because it is similar in structure to acetylcholine **[22,23]**. Acetyl-L-carnitine (ALC), is a constructive molecule in fatty acid metabolism and an agent potentially effective for treating peripheral neuropathic pain (PNP). Its effect, however, remains uncertain. Sima Anders et al. **[23]** and De Grandis and Minardi **[24]** demonstrated efficacy of ALC in reducing NP in patients with diabetic neuropathy. Other studies, including a meta-analysis **[25]**, showed ALC was effective in reducing visual analogue scale (VAS) in diabetes-related neuropathy. Other studies **[26-28]**

compared electromyographic findings in patients treated with ALC to results in not treated patients, suggesting an improvement in the treated group. Onofrj et al. and Memeo et al. **[29,30]** reported improvement of sciatic pain using ALC. Alpha-lipoic-acid (ALA) plays a possible effective role in reducing pain as well, being an antioxidant protecting damaged nerves **[31,32,33]**.

Observational pilot study

Based on the cited evidences on efficacy of these ingredients in treatment of NP, we performed an observational study to evaluate the efficacy of combined Uridine Monofosphate, acetyl-L-carnitine and Alpha-lipoic-acid in reducing pain even in chronic radiculopathy.

Methods

Patients referring to our neurological outpatient service and suffering from radiculopathy were prospectively recruited. Our inclusion criteria were:

1.age between 18 and 65 years

2.clinical diagnosis of chronic lumbar or cervical radiculopathy

3.presence of chronic pain assessed by Visual Analog Scale for Pain (VAS Pain) between 6 and 10

4. Evidence of radiculopathy at electromyography at T0

Treatment with combined uridine monophosphate-acetyl-L-carnitine and alpha lipoic acid was administrated orally respectively at daily dosage of 110 mg/die, 1000 mg /die and 600 mg /die for a 4 months period.

Follow-up visits were scheduled respectively three months (T90) and four months (T120) after treatment initiation (T0). VAS was administrated at T0, T90 and T120. At T120 a EMG was also performed

Results

Of the 1340 consecutive patients evaluated at our Outpatient Primary Care 60 patients (20 M, 40 F) were enrolled: 30 patients (9M, 21F) received the treatment and 30 patients (11M, 19F) were included in not-treated group control. In the treated group at T90 28/30 (93%) patients had a pain response to treatment with a reduction in VAS of at least 3 points, 2/30 (7%) had no pain response to treatment of at least 1-2 points; at T120 28/30 (93%) patients continued to have a pain response to treatment with a reduction in VAS of at least 3 points; 2/30 (7%) had no pain response to treatment of at least 1-2 points; at T120 27/30 (90%) had performed the prescribed control EMG and of these 3/27 (11%) had had an improvement in EMG parameters compared to EMG at T0. In the control group at T90 27/30 (90%) patients had no pain changes over the months, whereas 1/30 (3%) had a spontaneous 4-point VAS improvement after physiotherapy; 2/30 (7%) had worsening pain; at T120 26/30 (86.6%) patients had had no change in pain over the months; 1/30 (3.4%) continued to have spontaneous and stable improvement in the VAS. 1/30 (3.4%) continued to have spontaneous and stable improvement in the VAS scale; 3/30 (10%) had worsening pain; at T120 19/30 (63%) had performed the prescribed control EMG and of these 0/19 (0%) had had an improvement in EMG parameters at 120 days

Statistical analysis

The two groups were tested for homogeneity of initial conditions based on collected data (gender, age, ongoing physiotherapy, ongoing drug treatment, and initial VAS score). Tests used was according to data type (Chi squared, t-test, Wilcoxon test) and all resulted in homogeneous initial conditions with p-values well above 20%. VAS scores for the two groups were repeated at T90 and T120 and statistical analysis brought to the following conclusions:

1. The two groups behave differently in time (Wilcoxon test p.value < 0.001)
2. Treatment group VAS score changed significantly in time (Friedman test p.value < 0.001)
3. Control group VAS score did NOT change significantly in time (Friedman test p.value =0.62)
4. In treatment group there is a significant change (decrease) of VAS score between T0 and T90 (Wilcoxon test p.value < 0.001)
5. In treatment group, the improvement in VAS score is stable at T120 (no significant variation between T90 and T120, Wilcoxon test p. value =1)

Moreover for some patients in each group, EMG improvement was also evaluated at the end of the trial. No improvement was noted within patient belonging to the control group while 3 patients from treated group did show

an improvement. However the difference is not statistically significative between the two groups (binomial test p.value = 0.16). Given the observed EMG improvement observation (12.5%) to have enough statistical evidence, the trial should be repeated with at least 45 patient per group.

Conclusion

Polyneuropathies and entrapment neuropathies are a common cause of pain and disability. Radiculopathy as well is a common neurological disorder resulting from nerve root mechanical compression and/or irritation. These conditions may cause significant discomfort and functional deficits for the patients. Non operative management of radiculopathy is still not well defined and a protocol has not yet been established. As shown in literature, Uridine Monofosphate, but also acetyl-L-carnitine and Alpha-lipoic-acid can be effective in reducing pain intensity and associated symptoms and there is evidence demonstrating the effectiveness of any single of these three supplements. Data presented in our study on combination of Uridine Monofosphate, acetyl-L-carnitine and Alpha-lipoic-acid administrated in patients suffering from radiculopathy shown undoubtedly that pain decreased significantly in the treated group, leading to statistically significant improvement both in Friedman test and Wilcoxon test. Moreover, pain improvement was stable after 120 days during the treatment. Investigating evidence-based recommendations on no surgical treatment of cervical and lumbar radiculopathy, besides physiotherapy, there are many drugs used for pain relief but they can have side effects or contraindications. The role of nutraceutics and supplements as additional tool for treating chronic pain has grown up in popularity in the past 10 years. This survey suggests that this specific combination (Uridine Monofosphate, acetyl-L-carnitine, Alpha-lipoic-acid) can be a valid causal treatment in radiculopathy. However these results should be tested and confirmed in an adequately powered controlled trial.

Ethical standards

"All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants
included in the study."

Disclosure

"I certify that there is no actual or potential conflict of interest in relation to this article"

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